**Protocol/Amendment No.:** Protocol Version 3.0 Date: 02/02/2017

TITLE: A Pilot Study of MK-3475 with Cryotherapy for Men with Newly Diagnosed Oligo-

Metastatic Prostate Cancer

Johns Hopkins Kimmel Cancer Center

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#### 1.0 TRIAL SUMMARY

Abbreviated Title	MK-3475 and Cryotherapy for treatment of Metastatic
	Prostate Cancer
Trial Phase	Pilot
Clinical Indication	Metastatic Prostate Cancer
Trial Type	Single-arm open-label phase 2 trial
Type of control	None
Route of administration	IV
Trial Blinding	N/A
Treatment Groups	Single arm (MK-3475 with Cryotherapy and intermittent ADT)
Number of trial subjects	12
Estimated duration of trial	2 years (accrual and follow up)
<b>Duration of Participation</b>	1 year

#### 2.0 TRIAL DESIGN

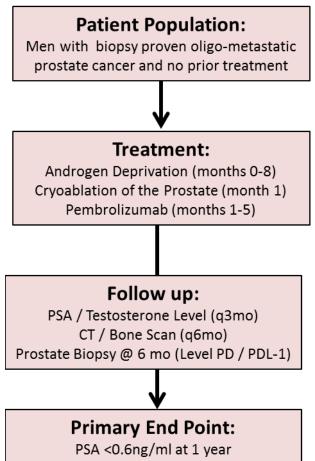
#### 2.1 Trial Design

This will be a single-arm open-label phase-2 trial for men with newly diagnosed oligometastatic prostate cancer who are eligible for cryotherapy.

Current standard of care for men with newly diagnosed metastatic prostate cancer involves continual or intermittent androgen deprivation. These regimens historically result in less than 25% of men (12% in the most recently reported large study) achieving an undetectable PSA (<0.2 ng/ml) at 1 year (Sweeney et al ASCO 2014). Patients on this study will be treated with a single course of intermittent androgen deprivation therapy (ADT) utilizing Degerelix for 8 months. One month following initiation of ADT, patients will undergo whole gland cryoablation of the prostate. All patients will receive Pembrolizumab 200mg every 3 weeks, starting at the time of cryoablation and continuing for 4 months q 3 weeks (for a total of 6 doses). PSA levels will be measured every 3 months with bone scan and CT or MRI scan performed at 6 month intervals. A prostate biopsy will be performed at the 6 month mark. Biopsy specimens will be assessed for PD-1 and PD-L1, along with CD8, CD4, FoxP3 and Ki67, using standard IHC methods available in the cancer center core. Staining will be compared to the pre-treatment diagnostic biopsies. The primary efficacy end point will be the proportion of men with PSA <0.6ng/ml at one year following initiation of treatment.

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#### 2.2 Trial Diagram



# 3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

- 3.1 Primary Objective(s) & Hypothesis (es)
- (1) **Objective:** Assess feasibility via the proportion of men reaching a low PSA nadir (<0.6ng/ml) at 1 year.
  - **Hypothesis:** Cryoablation combined with MK-3475 and intermittent androgen deprivation will result in an increased percentage of metastatic patients achieving a PSA nadir of <0.6ng/ml at 1 year.
- (2)**Objective**: Evaluate the safety of cryotherapy to the prostate combined with Pembrolizumab.
  - **Hypothesis**: The combination of cryoablation of the prostate with MK-3475 (Pembrolizumab) with standard of care treatment (intermittent androgen blockade) will be well tolerated by patients, with minimal Grade 3 or 4 toxicities.

# 3.2 Exploratory Objective

(1) **Objective:** To evaluate the effects of combination cryotherapy / pembrolizumab on PD-1 and PD-L1 expression in the prostate as assessed by biopsy performed 6 months post treatment.

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#### 4.0 BACKGROUND & RATIONALE

#### 4.1 Background

#### 4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [1]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [2; 3; 4; 5; 6]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated Tcells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [7; 8]. The structure of murine PD-1 has been resolved [9]. PD-1 and its associated family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosinebased switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade [7; 10; 11; 12]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins [13, 14]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, Treg and Natural Killer cells [15; 16]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [17]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [18, 19, 20, 13]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [13]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL) [21]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

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MK-3475 (previously known as SCH 900475) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

#### 4.1.2 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure for Preclinical and Clinical data.

#### 4.2 Rationale

#### 4.2.1 **Rationale for the Trial and Selected Subject Population**

For men with localized prostate cancer, primary treatment with radiation therapy or surgery represents standard-of-care therapy with defined efficacy. For men who present with oligo-metastatic disease, the standard treatment is systemic therapy with androgen-ablating drugs; a regimen associated with substantial morbidity and mortality, and with only a modest benefit in terms of long-term survival. Indeed the prognosis for men who initially present with metastatic disease is not especially favorable; a recent Eastern Cooperative Oncology Group (ECOG) study showed that these men have a 3-year overall survival (OS) of only 50%, which may be slightly improved by early administration of docetaxel-based chemotherapy. Indeed, an effective treatment for men who present with oligo-metastatic prostate cancer

# represents an unmet medical need.

One alternative treatment for such men may be a combination of cryotherapy (which ablates the prostate in situ, and which is associated with only minimal morbidity) with immunemodulation. We (Levy, Drake, Fuchs et al. J Pharmacol Exp Therapeutics 2009) and others (Waitz and Allison et al. Cancer Research 2012) showed that cryotherapy has immunestimulating properties. In carefully controlled studies in a prostate cancer model, the Allison group showed that combining immune checkpoint blockade with cryotherapy of a single lesion could prevent establishment of a second distant metastasis. Our group has experience in this regard, having completed a small proof-of-concept study combining cryotherapy with immunomodulatory dosing of cyclophosphamide in men with metastatic prostate cancer (Sidana et al *Urology* 2010).

While the optimal immunomodulating agent to combine with cryotherapy is the subject of ongoing preclinical experimentation, in some respects PD-1 blockade with pembrolizumab represents a nearly ideal companion for cryotherapy because of its documented clinical efficacy in multiple tumor types, its acceptable toxicity profile, and the notion that prostate cancer cells can express PD-L1 upon stimulation with appropriate cytokines in vitro (Drake et. al., unpublished). We thus propose that: cryotherapy for prostate cancer can be administered in combination with PD-1 blockade, and that this combination may mediate systemic responses in distant lesions.

Though we feel that the rationale is sound and pre-clinical evidence is promising, the informed consent process will specifically inform patients that cryotherapy either alone or in combination with MK-3475 and androgen deprivation represents a non-standard approach to metastatic disease and that no studies have shown that cryotherapy will be beneficial in this setting. We will also inform patients that cryoablation can be associated with irreversible side effects, most notably the inability to maintain erection and in some cases with incontinence.

### 4.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated

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three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. Recent data from other clinical studies within the MK-3475 program have shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 - 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings and a fixed dose of 200mg every 3 weeks will be chosen for this investigation.

#### 4.2.3 Rationale for Endpoints

#### 4.2.3.1 Efficacy and Safety Endpoints

Efficacy endpoints include a PSA of <0.6ng/ml at 12 months. This level of PSA has previously been shown to indicate cure in men with localized prostate cancer treated with prostate cryoablation (Levy et al J Urol 2009). The proportion of men with PSA <0.6ng/ml at 1 year after undergoing cryoablation with MK-3475 and intermittent androgen deprivation will be compared to historical controls (12% of men treated with androgen deprivation alone in the recently reported CHAARTED trial achieved an undetectable PSA (<0.2ng/ml) at 1 year when on androgen deprivation alone) (Sweeney et al *ASCO* 2014). Treatment failures will include those men with persistently rising PSAs as well as those developing new metastatic disease on imaging at the 6 and 12 month assessments. Men with stable low PSAs but not reaching <0.6ng/ml will be considered partial responders.

A co-primary end point will be safety. Here, more than 2 clinically significant (i.e. non-laboratory) grade IV or any grade V event will prompt ending of the trial and a claim of futility.

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#### 4.2.3.2 Biomarker Research

We hypothesize that the combination of cryotherapy and pembrolizumab will promote an immune infiltrate, enriched in CTLs, into the prostate and that the extent of this infiltrate will correlate with clinical response. PD-1 and PD-L1 levels in the prostate as well as the immune infiltration into the prostate will be examined by immuno-histochemistry (IHC). IHC utilizing antibodies directed against PD-1, PD-L1, CD8, CD4, FoxP3 and Ki67 will be used for staining on prostate biopsy tissue obtained before treatment and at 6 months following initiation of treatment.

#### 5.0 METHODOLOGY

#### 5.1 Entry Criteria

#### 5.1.1 Diagnosis/Condition for Entry into the Trial

Men entering into the trial are required to have oligo-metastatic prostate cancer with no prior treatment. Oligo-metastatic disease will be defined as <5 extra-pelvic metastasis. The metastatic lesions may be lymph nodes, with pathological enlargement considered if greater than 10mm in size along the longest axis.

#### 5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

- 1. Have histologically or cytologically diagnosed oligo-metastatic prostate cancer. Oligo-metastatic disease is defined to reflect men with low volume disease. Specifically, oligo-metastatic disease is defined as less than 5 extra-pelvic metastases. Metastatic lesions may be lymph nodes.
- 2. Be willing and able to provide written informed consent/assent for the trial.
- 3. Be  $\geq$  18 years of age on day of signing informed consent.
- 4. Have available tissue from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion.
- 5. ECOG Performance Scale status of 0 or 1.
- 6. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 14 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Serum creatinine <b>OR</b>	≤1.5 X upper limit of normal (ULN) <b>OR</b>
Measured or calculated <sup>a</sup> creatinine	
clearance (GFR can also be used in	$\geq$ 60 mL/min for subject with creatinine levels $\geq$ 1.5 X institutional
place of creatinine or CrCl)	ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN <u><b>OR</b></u>
	Direct bilirubin $\leq$ ULN for subjects with total bilirubin levels $> 1.5$
	ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN <u><b>OR</b></u>
AST (SOOT) and ALT (SOPT)	≤ 5 X ULN for subjects with liver metastases

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Coagulation				
or Prounrombin Time (PT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants			
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants			
<sup>a</sup> Creatinine clearance should be calculated per institutional standard.				

- 7. Subjects who have been on hormonal therapy up to 30 days prior to enrollment and receiving Degarelix are allowed to be on the study.
- 8. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

### 5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

- 1. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of treatment.
- 2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
- 3. Has had a prior monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
- 4. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.
  - Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.
  - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
- 5. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.
- 6. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment.
- 7. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study.

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8. Has evidence of interstitial lung disease or active, non-infectious pneumonitis.

- 9. Has an active infection requiring systemic therapy.
- 10. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
- 11. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
- 12. Is expecting to father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
- 13. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
- 14. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
- 15. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
- 16. Has received a live vaccine within 30 days prior to the first dose of trial treatment.
- 17. Has severe voiding symptoms (IPSS >20) or urinary retention requiring a catheter
- 18. Has contraindications to cryotherapy of the prostate, including: previous TURP with persistent TUR defect, existing peri-anal or recto-urethral fistula, previous external beam radiation therapy or brachytherapy, coagulopathy, inability to tolerate anesthesia (spinal or general), inability to tolerate transrectal ultrasound (i.e. history of previous abdominal perineal resection).

#### 5.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table 2. In regards to cryotherapy, whole gland cryoablation will be performed using an argon/helium gas-based system (in this study the Endocare cryoablation system will be used). After the patient is placed under anesthesia and into lithotomy position and peri-operative antibiotics are given, a trans-rectal ultrasound probe will be entered for volume mapping. Cryoablation probes and thermocouple sensors will then be inserted (with thermocouple probes in the Denovillier's fascia and at the external striated sphincter). After cystoscopy to demonstrate no probe intrusion into the urethra or bladder, a warming catheter will be inserted. Two cycles of cryoablation will be performed under transrectal ultrasound monitoring to documented temperatures below -40 degrees Celsius. Following these two freeze / thaw cycles the warming catheter will be left in place for an additional 15-20 minutes. The warming catheter will be replaced by a foley catheter. Catheters will be removed at 10-15 days post treatment and a voiding trial performed.

Table 2 Trial Treatment

Drug/	Dose/Potency	Dose	Route of	Regimen/Treatment	Use	
Procedure		Frequency	Administration	Period		
MK-3475	200mg	Q3 weeks	IV infusion	4 months (starting 1	Experimental	
				month after ADT)		
Degarelix	240mg	Q1mo	SQ injection	8 months	Standard of	
	loading, 80mg				Care	
	maintenance					

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Drug/	Dose/Potency	Dose	Route of	Regimen/Treatment	Use	
Procedure		Frequency	Administration	Period		
Cryotherapy N/A Once N/A		Cryoablation of the	Experimental			
			prostate occurring 1			
			month after initiation			
of ADT						
The MK-3475 dosing interval may be increased due to toxicity as described in Section 5.2.1.2.						

#### **5.2.1** Dose Selection/Modification

#### **5.2.1.1** Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale.

#### **5.2.1.2** Dose Modification

MK-3475 will be withheld for drug-related Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 3 including laboratory abnormalities, and severe or life-threatening AEs as per Table 3 below.

Table 3: Dose modification guidelines for drug-related adverse events.

Toxicity Hematological Toxicity	Grade  1, 2  3*  *Excluding Grade 3 neutropenia, anemia, and thrombocytopenia	Hold Treatment (Y/N) No Yes	Timing for restarting treatment N/A Toxicity resolves to Grade 0-1 or baseline	Dose/Schedule for restarting treatment N/A May increase the dosing interval by 1 week	Discontinue Subject (after consultation with Sponsor) N/A Toxicity does not resolve within 12 weeks of last infusion Permanent discontinuation
	4	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week	should be considered for any severe or life-threatening event
Non-hematological toxicity	1	No	N/A	N/A	N/A
Note: Exception to be treated similar to grade 1 toxicity Grade 2 alopecia Grade 2 fatigue  For additional information	2	Consider withholding for persistent symptoms	Toxicity resolves to Grade 0-1 or baseline	Clinical AE resolves within 4 weeks: Same dose and schedule Clinical AE does	Toxicity does not resolve within 12 weeks of last infusion
For additional information regarding Adverse Events with a potential Immune-Etiology reference, please see the separate				not resolve within 4 weeks: May increase the dosing interval by 1 week for each occurrence	

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Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject (after consultation with Sponsor)
Pembrolizumab Event of Clinical Interest Guidance Document.	3,4	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week for each occurrence	Toxicity does not resolve within 12 weeks of last infusion Permanent discontinuation should be considered for any severe or life-threatening event

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, trial treatment will be considered for discontinuation. Subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled. As it is unknown whether MK-3475 will increase the local toxicity of cryotherapy, we will specifically assess for local toxicity prior to each infusion of drug. This includes assessment of pelvic pain, genital swelling, new incontinence, urinary retention and recto-urethral fistulas. If these toxicities are present and worsening with MK-3475 re-challenge the subject will be discontinued from trial treatment.

Subjects who experience a recurrence of the same severe or life-threatening event at the same grade or greater with re-challenge of MK-3475 should be discontinued from trial treatment.

### **5.2.2** Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

MK-3475 will be administered as a 30 minute IV infusion (treatment cycle intervals may be increased due to toxicity as described in Section 5.2.1.2). Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

#### 5.2.3 Trial Blinding/Masking

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

#### 5.3 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or

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vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the Investigator, the Sponsor, and the subject.

#### **5.3.1** Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

#### 5.3.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Anti-cancer systemic chemotherapy or biological therapy beyond that specified in this protocol
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than MK-3475
- Radiation therapy
  - o Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with Sponsor.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed..
- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications which are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

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#### 5.4 Rescue Medications & Supportive Care

#### **5.4.1** Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below:

- Diarrhea: Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic subjects, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.
  - o In subjects with severe enterocolitis (Grade 3), MK-3475 will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.
  - o In subjects with moderate enterocolitis (Grade 2), MK-3475 should be withheld and anti-diarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. Regarding guidelines for continuing treatment with MK-3475, see Section 5.2.
  - All subjects who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
- Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.
- Anti-infectives: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.
- Immune-related adverse events: Please see the separate guidance document regarding diagnosis and management of adverse experiences of a potential immunologic etiology.
- Management of Infusion Reactions: Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting.

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Table 5 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of MK-3475.

Table 5 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	Stop Infusion and monitor symptoms.  Additional appropriate medical therapy may include but is not limited to:  IV fluids  Antihistamines  NSAIDS  Acetaminophen  Narcotics  Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.  If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose.  Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of MK-3475 with:  Diphenhydramine 50 mg po (or equivalent dose of antihistamine).  Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)  Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. Subject is permanently discontinued from further trial treatment administration.	No subsequent dosing
administration.	uld be available in the room and a physician readily a he Common Terminology Criteria for Adverse Event	

# 5.4.1.1 Supportive Care Guidelines for Events of Clinical Interest and Immune-related Adverse Events (irAEs)

Events of clinical interest of a potential immunologic etiology (irECIs) may be defined as an adverse event of unknown etiology, associated with drug exposure and is consistent with an

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immune phenomenon. irAEs may be predicted based on the nature of the MK-3475 compound, its mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as an irAE. Information on how to identify and evaluate irAEs has been developed and is included in the Pembrolizumab Event of Clinical Interest Guidance Document.

# 5.5 Diet/Activity/Other Considerations

#### 5.5.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

#### 5.5.2 Contraception

MK-3475 may have adverse effects on a fetus in utero. Furthermore, it is not known if MK-3475 has transient adverse effects on the composition of sperm. Men engaging in intercourse with a sexual partner able to conceive should use at least 2 methods of birth control. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 7.2.2-Reporting of Pregnancy to the Sponsor and to Merck. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

#### 5.6 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

A subject must be discontinued from the trial for any of the following reasons:

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• The subject or legal representative (such as a parent or legal guardian) withdraws consent.

- Unacceptable adverse experiences
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Trial Flow Chart) and Section 7.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

# 5.7 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

- 1. Quality or quantity of data recording is inaccurate or incomplete
- 2. Poor adherence to protocol and regulatory requirements
- 3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
- 4. Plans to modify or discontinue the development of the study drug

In the event of Merck decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

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# 6.0 TRIAL FLOW CHART

#### Study Flow Chart 6.1

Trial Period	Screening Phase		tment itment				ks)	End of MK- 3475	Post-Treat	ment
Treatment Cycle/Title	Screening	1	2	3	4	5	6	Discont.	Safety Follow up	Follow up
Scheduling Window	-28 to -1	<u>+</u> 3 d	ays for	all	1			At time of Discont.	30d post MK-3475	Every 12 weeks post ADT*
Administrative Procedures										
Informed Consent	X									
Inclusion/Exclusion Criteria	X									
Medical History	X									
Post-study anticancer therapy status										X
Survival Status										X
Clinical Procedures/Assessn	nents			T	ı	T		ı		
Cryoablation of the Prostate		X								
Androgen Deprivation Therapy (8 months total)				Х						
Pembrolizumab (MK-3475) Administration		X	X	X	X	Х	X			
Review Adverse Events (including local symptoms: pelvic pain, swelling, incontinence, fistula)		X	X	X	X	X	X	X	X	X
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X	X	X	
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	X	X	X	X	
Laboratory Procedures / Ass	sessments: an	alysis pe	rforn	ed by	LOCA	AL lab	orato	ory		
PT/INR and aPTT	X**								X	
CBC with Differential	X**	X	X	X	X	X	X	X	X	
Chemistry Panel	X**	X	X	X	X	X	X	X	X	
Urinalysis	X**									
T3, FT4 and TSH	X**		X		X		X	X	X	
<b>Efficacy Measurements</b>										
PSA	X****				X				X	X
Tumor Imaging (BS/CT)	X****								X	X***
Tumor Biopsies/Archival Tiss		orrelativo	Stud	ies Blo	od					
Archival or Newly Obtained Tissue -TRUS guided prostate biopsy	X									
TRUS guided prostate biopsy Research Biopsy									X	
Blood for (lymphocytes) and serum for immunological Studies	Х		X		Х		X	X	Х	

<sup>\*</sup>Every 12 weeks post ADT up to 1 year

<sup>\*\*</sup>Screening Lab tests for determining eligibility are to be performed within 10 days prior to the first dose of (MK-3475).
\*\*\* Imaging assessment by bone scan and CTor MRI scan will be every 6 months.

<sup>\*\*\*\*</sup> Initial scans and PSA should be performed within 60 days of starting MK3475

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Table 6: Study flow chart

#### 7.0 TRIAL PROCEDURES

#### 7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator. Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or Merck for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

#### 7.1.1 Administrative Procedures

#### 7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial. Importantly, the informed consent will specifically state that cryotherapy, either alone or in combination with MK-3475, is not a standard treatment approach for metastatic prostate cancer. No studies have shown that cryotherapy, either alone or in combination with MK-3475, is beneficial in this setting and cryotherapy may be associated with certain irreversible side effects such as inability to maintain an erection or inability to retain urine.

#### 7.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

#### 7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

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#### 7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card after the subject provides written informed consent.

#### 7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

#### 7.1.1.5 Prior and Concomitant Medications Review

#### 7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

#### 7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

#### 7.1.1.6 Disease Details and Treatments

#### 7.1.1.6.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

#### 7.1.1.6.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

#### 7.1.1.6.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

#### 7.1.1.7 Assignment of Screening Number

Subjects will be assigned a screening number at the time of the screening visit.

#### 7.1.1.8 Trial Compliance (Medication/Diet/Activity/Other)

Trial compliance will be assessed at treatment and post treatment visits.

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#### 7.1.2 Clinical Procedures/Assessments

#### 7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 12.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs of unknown etiology associated with MK-3475 exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (irAE). See the separate Pembrolizumab Event of Clinical Interest Guidance Document.

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

#### 7.1.2.2 Physical Exam

The investigator or qualified designee will perform a physical exam during the screening period and prior to trial treatment administration. Clinically significant abnormal findings during the screening period should be recorded as medical history.

## 7.1.2.3 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

### 7.1.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 12.4) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

#### 7.1.2.5 Tumor Imaging and Assessment of Disease

Tumor imaging by bone scan and CT or MRI scan will begin following discontinuation of treatments (6 months after trial initiation). Bone scan and CT or MRI of the abdomen and pelvis will be performed every 6 months; roughly at the 6 month (time of discontinuation) and 12 month marks. PSA will also be tested at this time interval.

#### 7.1.2.6 Tumor Tissue Collection

Transrectal prostate biopsy will be performed at the 6 month mark to be used for correlative studies (immune-histochemistry).

#### 7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

#### 7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 7.

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Table 7 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	PT (INR)
Hemoglobin	Alkaline phosphatase	Glucose	аРТТ
Platelet count	Alanine aminotransferase (ALT)	Protein	Total thriiodothyronine (T3)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Free tyroxine (T4)
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam (If abnormal)	Thyroid stimulating hormone (TSH)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	PK
	(CO <sub>2</sub> or biocarbonate)		Prostate Specific Antigen (PSA)
	Uric Acid		
	Calcium		Blood for Correlative Studies
	Chloride		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin (If total bilirubin is elevated above the upper limit of normal)		
	Total protein		
	Blood Urea Nitrogen		

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Laboratory tests for screening should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

### 7.1.3.2 Research blood samples Evaluations

#### 7.1.3.2.1 Blood Collection for Peripheral blood lymphocytes

Peripheral blood lymphocytes (PBLs) will be obtained by collecting 50 mL of blood drawn by 60cc syringes into a 50 mL heparinized conical tube. PBLs will be prepared by Ficoll-Hypaque density gradient centrifugation according to standard protocols, and will be cryopreserved in a liquid nitrogen freezer at –140°C for further batched analyses.

The time points for Peripheral blood lymphocytes are described in Section 6 – Trial Flow Chart.

#### 7.1.3.2.2 Blood Collection for Sera for Immunoassays

At each time point (baseline/screening, Cycle 2, Cycle 4, Cycle 6, at time of Discontinuation and 30 day post MK-3475), the following research blood samples should be collected and processed as outlined below:

- Draw approximately 10 mL of peripheral blood into 2 plain (red top) or SST (gold top) tubes, each containing ≥5 mL of blood per vacutainer.
- Allow blood to coagulate for 20 minutes, then centrifuge at 25oC, 1500 x g (2700-3000 rpm), for 15 minutes.
- Pipette the serum into 10 cryotubes (about 0.5 mL/tube).
- Store cryotubes frozen, below –20oC (–70oC preferred), until the time of analysis.

#### 7.1.4 Other Procedures

#### 7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. After discontinuing treatment, subjects should return to the site for a Safety Follow-up Visit and then proceed to the Follow-Up Period of the study.

#### 7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

#### 7.1.5.1 Screening

Screening will occur after patients are identified via routine clinic visits to Urology, Medical Oncology or Radiation Oncology.

#### 7.1.5.2 Treatment Period

Treatment will consist of androgen deprivation, MK-3475 and cryoablation of the prostate. - Degarelixwill begin after the main screening visit. One month following androgen deprivation,

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patients will undergo cryoablation of the prostate and additionally begin treatment with MK-3475. MK-3475 will continue for 6 treatments. Androgen deprivation will continue until the 6 month mark

#### 7.1.5.3 Post-Treatment Visits

Following treatment, men will be evaluated at 12 week intervals up to the one year mark following initiation of treatment. Evaluation will include following the post-study anticancer therapy status and the survival status as described in the table above. Following cryoablation of the prostate, men will have an indwelling catheter which will be removed 2 weeks later in the Urology clinic.

# 7.1.5.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

# 7.1.5.4 Follow-up Visits

Subjects who discontinue trial treatment will move into the Follow-Up Phase and should be assessed every 12 weeks ( $\pm$  7 days) to follow the post-study anticancer therapy status and the survival status. Radiologic imaging assessment will be every 6 months to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death or end of the study.

#### 7.1.5.4.1 Survival Follow-up

Once a subject experiences confirmed disease progression (defined as 2 consecutive PSA elevations) or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

#### 7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Merck's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples

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of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

Adverse events may occur during the course of the use of Merck product in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

# 7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for MK-3475 by 20% over the prescribed dose. No specific information is available on the treatment of overdose of MK-3475. In the event of overdose, MK-3475 should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

#### 7.2.2 Reporting of Pregnancy to the Sponsor and to Merck

Although pregnancy is not considered adverse events, it is the responsibility of investigators or their designees to report pregnancy in a subject's partner within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy

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outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

#### 7.2.3 Immediate Reporting of Adverse Events to the Sponsor and to Merck

#### 7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Merck's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is another important medical event

Refer to Table 8 for additional details regarding each of the above criteria.

Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

Non-serious Events of Clinical Interest will be forwarded to Merck Global Safety and will be handled in the same manner as SAEs.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck.

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220

#### JHM IRB reporting:

Serious adverse events and protocol problems (e.g. protocol deviations, non-adherence) will be reported in compliance with JHMI.

IRB guideline, "Organization Policy on Reports of Unanticipated Problems

Involving Risks to Participants or Others" [Policy No. 103.6(b)] (most current version). A copy of this document is located at

http://www.hopkinsmedicine.org/institutional\_review\_board/guidelines\_policies/organization\_npolicies/103\_6b.html.

All deaths on study regardless of attribution must be reported to the JHM IRB.

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All subjects with serious adverse events must be followed up for outcome.

# **7.2.3.2** Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

Events of clinical interest for this trial include:

- 1. an overdose of Merck product, as defined in Section 7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
- 2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.\*
  - \*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).
- 3. In the event a subject develops any of the following AEs, a detailed narrative of the event should be reported as an ECI to the Sponsor within 24 hours and to Merck Global Safety within 2 working days of the event:
  - a. Grade > 3 diarrhea
  - b. Grade  $\geq 3$  colitis
  - c. Grade  $\geq 2$  pneumonitis
  - d. Grade  $\geq$  3 hypo- or hyperthyroidism

A separate guidance document has been provided entitled "Pembrolizumab Event of Clinical Interest Guidance Document." This document provides guidance regarding identification, evaluation and management of ECIs and irAEs. Additional ECIs are identified in this guidance document and also need to be reported to the Sponsor within 24 hours and to Merck Global Safety within 2 working days of the event.

Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

ECIs that occur in any subject from the date of first dose through 90 days following cessation of treatment, or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to the Merck's product, must be reported within 24 hours to the Sponsor and to Merck Global Safety within 2 working days.

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#### 7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

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Table 8 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE	Grade 1	latified physician, will evaluate all adverse events as to:				
Grading	Grade 1	Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.				
Grading	Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.				
	Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-				
	Grade 3	care ADL.				
	Grade 4	Life threatening consequences; urgent intervention indicated.				
	Grade 5	Death related to AE				
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:					
	†Results in deat	†Results in death; or				
		†Is life threatening; or places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or				
	†Results in a per	sistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions); or				
	precautionary m	†Results in or prolongs an existing inpatient hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or				
	†Is a congenital anomaly/birth defect (in offspring of subject taking the product regardless of time to diagnosis);or					
	Is a new cancer; (that is not a condition of the study) or					
		Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.				
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).					
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units					
Action taken	Did the adverse event cause the Merck product to be discontinued?					
Relationship to test drug	Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. The following components are to be used to assess the relationship between the Merck product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):					
	Exposure	Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count,				
	_	diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?				
	Time Course	Course  Did the AE follow in a reasonable temporal sequence from administration of the Merck product?  Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?				
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors				

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Relationship	The following components are to be used to assess the relationship between the test drug and the AE: (continued)				
to Merck product	Dechallenge	Was the Merck product discontinued or dose/exposure/frequency reduced?			
(continued)		If yes, did the AE resolve or improve?			
		If yes, this is a positive dechallenge. If no, this is a negative dechallenge.			
		(Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the			
		Merck product; or (3) the trial is a single-dose drug trial); or (4) Merck product(s) is/are only used one time.)			
	Rechallenge	Was the subject re-exposed to the Merck product in this study?			
		If yes, did the AE recur or worsen?			
		If yes, this is a positive rechallenge. If no, this is a negative rechallenge.			
		(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Merck			
		product(s) is/are used only one time).			
		NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY			
		THE MERCK PRODUCT, OR IF REEXPOSURE TO THE MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE			
		SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE			
		MODIFICATION GUIDELINES IN THE PROTOCOL.			
	Consistency with	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Merck product or drug class pharmacology or			
	Trial Treatment	toxicology?			
	Profile				
The assessment of r	elationship will be rep	orted on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration			
of the above elemen	nts.				
Record one of the following		Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Merck product relationship).			
Yes, there is a reas	sonable possibility of	There is evidence of exposure to the Merck product. The temporal sequence of the AE onset relative to the administration of the Merck product is			
Merck product relat		reasonable. The AE is more likely explained by the Merck product than by another cause.			
No, there is not a r	easonable possibility	Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR			
Merck product relationship		there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)			

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#### 7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

#### 8.0 STATISTICAL ANALYSIS PLAN

### 8.1 Statistical Analysis Plan Summary

The co-primary endpoints will be safety, determined as the rate of SAEs, and the proportion of patients with PSA (<0.6ng/ml) at 1 year. Exploratory endpoints include correlation of biopsy PD-1 and PD-L1 expression with PSA response and tumor response via imaging, as well as evaluating whether expression is associated with other clinical or patient characteristics.

#### 8.2 Statistical Analysis Plan

Co-primary endpoints.

Safety: We will not separately evaluate cryotherapy alone, or ADT alone because they have well-established excellent safety profiles in this clinical setting. Additionally, we will not include an arm with Pembrolizumab dose escalation because the approved dose has already been established. We will monitor all patients for AEs, and calculate the proportion of patients with AEs by grade. The trial will be stopped if more than 2 clinically significant (i.e. non-laboratory) grade IV or any grade V event occurs.

Efficacy: In this 12 man study, the minimum expectation to continue will be that 30% of men reach the primary endpoint (PSA of 0.6ng/ml at 1 year with a detectable testosterone). The recently reported results from the CHAARTED study indicate that among men presenting with metastatic prostate cancer (without prior local treatment (73% of the cohort)) 11.7% will reach a PSA of <0.2ng/ml with continuous androgen deprivation alone at the one year mark. No evidence exists regarding the treatment of oligo-metastatic men with cryotherapy of the prostate alone - however it can be assumed that none of these men would achieve PSA <0.2 ng/ml at the one year mark. Evidence does exist in the primary prostate cancer treatment setting for localized disease and suggests that a PSA nadir of <0.6ng/ml after cryo-ablation indicates excellent local control (Levy et al J Urol 2009).

The proportion of men with oligo-metastatic disease undergoing a combination of cryotherapy with Pembrolizumab and short term androgen blockade who reach a PSA of <0.6ng/ml at one year is unknown, and there is a paucity of PSA response data for other combination treatments in this setting. Stereotactic body radiation (SBRT) +/- androgen deprivation has achieved good responses with oligo-metastatic disease. In one study PSA data were available. Five patients had PSA levels recorded at 12 months or greater post-SBRT, and an additional 2 patients had PSA increasing within <12 months. Among these 7 patients 2 (29%) had PSA<0.1 ng/ml at ≥12 months (Ahmed et al 2013). All 7 patients also received ADT after SBRT. This provides a conservative estimate of the minimum response rate we would like to observe in our trial to warrant further development of our proposed treatment regimen ("conservative" because 5 additional patients achieved PSA <0.1 at last follow-up <12 months and are not included among the 7 patients on whom the 29% rate is calculated and because these patients were on continual ADT).

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% undetectable PSA at 1	Lower 95% confidence	Lower 95% confidence
year	bound for n=12	bound for n=14
30%	.10	.11
35%	.13	.15
40%	.17	.18

We will determine the proportion of patients who achieve PSA <0.6ng/ml at 12 months. Patients who are unable to complete 12 months of follow-up due to AEs or worsening disease will be considered treatment failures and will be included in the intention to treat calculation of the proportion with undetectable PSA. The table shows the lower 95% confidence bound for different target proportions of undetectable PSA, including the minimum value of 30% derived above. Confidence interval bounds were calculated using PASS v11 (NCSS Software, Inc., Kaysville, UT). If promising results are seen, it would warrant further investigation in a larger, randomized Phase II trial.

#### Exploratory endpoints

Biopsy PD-1 and PD-L1: Expression of each biomarker will be correlated with proportion undetectable PSA using logistic regression, and with change in tumor burden using ANOVA or Kruskal-Wallis. Analyses to correlate expression with other binary or continuous clinical parameters will be similarly performed.

# 9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

#### 9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by Merck as summarized in Table 10.

Table 10 Product Descriptions

Product Name & Potency	Dosage Form
MK-3475 100 mg/ 4mL	Solution for Injection

#### 9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Effective January 2017, marketed packs of the Investigational Product will be supplied for study use. As such, Merck will not supply any Chemistry, Manufacturing, Control (CMC) information. Investigator's regulatory submission should reference the Merck Marketing Authorization. If any additional labeling of containers is required, e.g. to add Study Protocol number, and it has not been agreed for Merck to perform the additional labeling, it is the investigator's responsibility to arrange for this action to be done in accordance with U.S. regulations.

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#### 9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

### 9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

#### 9.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

#### 10.0 ADMINISTRATIVE AND REGULATORY DETAILS

### 10.1 Confidentiality

The investigator agrees to keep all information provided by MERCK in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by MERCK (investigators' brochures and other material) will be stored appropriately to ensure their confidentiality. The information provided by MERCK to the investigator may not be disclosed to others without direct written authorization from MERCK, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

#### **10.2** Compliance with Financial Disclosure Requirements

Investigators will provide disclosure of all financial relationships with MERCK or other companies to patients enrolling in the trial and additionally on any publications resulting from this study.

#### 10.3 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and

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pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

#### **10.4 Quality Management System**

The quality of data collection will be routinely monitored by the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center (SKCCC) Data and Safety Monitoring Committee.

#### 10.5 Data and Safety Monitoring

This is a DSMP Level II study under the SKCCC Data and Safety Monitoring Plan (12/6/2012). Data Monitoring of this protocol will occur on a regular basis with the frequency dependent on the rate of subject accrual and the progress of the study. The protocol will be monitored internally at SKCCC by the Principal Investigator and externally by the SKCCC CRO in accordance with SKCCC guidelines. Trial monitoring and reporting will be done through the Safety Monitoring Committee (SMC) at SKCCC.

Additionally, scheduled meetings will take place monthly and will include the protocol principal investigator, research nurse, data manager, and, when appropriate, the collaborators, subinvestigators, and biostatistician involved with the conduct of the protocol.

During these meetings the investigators will discuss matters related to: safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for secondary objectives.

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#### 12.0 APPENDICES

#### 12.1 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

<sup>\*</sup> As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

#### 12.2 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

# 12.3 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

RECIST version 1.1\* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

\* As published in the European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

In addition, volumetric analysis will be explored by central review for response assessment.